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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,440	03/30/2001	Lucio Miele	4239-58051	1318

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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET, SUITE #1600
ONE WORLD TRADE CENTER
PORTLAND, OR 97204-2988

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,440	MIELE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-18,22-24,26,27,30-32,72-75 and 80-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-18, 22-24, 26-27, 30-32, 72-75 and 80-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/30/01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 1-5, 8-18, 22-24, 26-27, 30-32, 72-75 and 80-86 are currently pending in the instant application. Applicants elected Group I, claims 1-3, 5, 7-14, 16, 26, and 72-75 directed to a method of inducing apoptosis in a cell by administering an oligonucleotide that antagonizes Notch-1 expression, with traverse. However, in light of Applicant's amendments and arguments, Claims 4, 15, 17-18, 22-24, 27, 30-32 and 80-86 will also be joined to the elected invention.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, lines 4, recites the phrase "exposing the cell an agent.." This phrase is grammatically incorrect. It is likely that Applicants intended the phrase to recite "exposing the cell to an agent."

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5, 8-15, 17-18, 22-24, 26-27, 30-32, 72-75 and 80-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

6. The instant claims are drawn to methods requiring the use of agents that interfere with Notch function or expression. The specification as filed describes antisense oligonucleotides according to SEQ ID NO: 6, 8 and 11 which target Notch-1, additionally the specification disclose antibodies targeting human Notch-1. However, the instant claims are drawn to a broad class of antisense oligonucleotides which interfere with the expression of gene sequences, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and sequences isolated from various organisms that encode a Notch protein. Additionally, the instant claims are broadly drawn to antagonizing agents, including antibodies that target all allelic and polymorphic forms of the Notch protein and gene sequence. The specification as filed provides insufficient written description to support the genus of agents, which interfere with the function of a Notch protein or expression of a Notch gene sequence, encompassed by the instantly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possess of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, 1116.)

With the exception of the antisense oligonucleotides according to SEQ ID NO: 6, 8 and 11, and the antibody targeting Notch-1, the skilled artisan cannot envision the detailed chemical

structure of the encompassed agents that interfere with Notch function or expression, regardless of the complexity or simplicity of the method of isolation of these agents. Adequate description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid antisense compounds, antibodies, and/or other agents are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Col. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cr. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention with all its claimed limitations, not that which makes it obvious," and by using "such descriptive meands as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d. at 1606.

The name cDNA is not itself a written description of that DNA; it conveys not distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating whcih nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only the antisense oligonucleotides according to SEQ ID NO: 6, 8, and 11 and the antibody targeting Notch-1, but not the full breadth of the claims (or none of the other agents

encompassed by the claims) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

7. Claims 1-5, 8-16, 26, 30-31, 72-75, 80, 82, and 84-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed methods in vitro comprising the administration of antisense agents that interfere with Notch expression, does not reasonably provide enablement for practicing the claimed methods in vivo comprising the administration of antisense oligonucleotide agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-5, 8-16, 26, 30-31, 72-75, 80, 82, and 84-86 embrace methods of antisense based therapy. The instant specification, and in particular claim 86, asserts that antisense agents can be administered to a subject such that said agent can interfere with the expression of Notch in a target cell, and wherein apoptosis is induced in said target cell. Furthermore, the specification as filed contemplates that use of this method for the treatment of cancers such as cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy. However, no specific guidance is provided for the delivery of sufficient antisense oligonucleotide to a particular cell type for amelioration or treatment of any particular disease. The guidance provided is cursory and provides no detail for any particular disease treatment, for example.

The art of nucleic acid based therapy is an unpredictable art. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity..[h]owever, they are far more difficult ot produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven." ; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose target sites are particularly vulnerable to attach. [t]his is a challenging quest. "; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents." [n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically.."..[unknown], "non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always need to establish a compound's primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its does-response curve and therapeutic index is known."; [c]ompared to the does response curves of conventional drugs, which typically span two to three orders of magnitude, those antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible in

vivo, effective antisense molecules must be determined empirically by screening lager numbers of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most sites. [s]ince accessibiltiy cannot be predicted, rational design of antisense molecules is not possible.'" and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition in vivo is beginning to be explored...[i]t is not yet clear whether in vitro screening techniques...will identify ODNs that are effective in vivo."

Jen et al. [STEM CELLS Vol. 18: 307-319, 2000] discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al. assert"[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome. One in the art would be required to perform undue trial and error experimentation to practice the claimed invention. The quantity of experimentation would include the determination of specific antisense sequences that

would be effective in vivo and how to deliver sufficient antisense to target cells of a disease contemplated for Notch antisense therapy, for example.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE